

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
31 July 2003 (31.07.2003)

PCT

(10) International Publication Number  
**WO 03/061657 A1**

(51) International Patent Classification<sup>7</sup>: **A61K 31/444**,  
A61P 1/04, C07D 471/04 // (C07D 471/04, 221:00,  
209:00)

(74) Agents: **SALIWANCHIK, David, R.** et al., Saliwanchik,  
Lloyd & Saliwanchik, 2421 N.W. 41st Street, Suite A-1,  
Gainesville, FL 32606-6669 (US).

(21) International Application Number: PCT/US03/01876

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,  
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,  
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,  
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,  
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,  
MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE,  
SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ,  
VC, VN, YU, ZA, ZM, ZW.

(22) International Filing Date: 21 January 2003 (21.01.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
60/350,504 18 January 2002 (18.01.2002) US

(71) Applicant (*for all designated States except US*): **ARYX  
THERAPEUTICS** [—/US]; 2255 Martin Avenue, Suite F,  
Santa Clara, CA 95050 (US).

(84) Designated States (*regional*): ARIPO patent (GH, GM,  
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),  
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),  
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,  
ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI,  
SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN,  
GQ, GW, ML, MR, NE, SN, TD, TG).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **ZHANG, Xiaming**  
[US/US]; 2290 Cervantes Way, Campbell, CA 95008 (US).  
**PFISTER, Jurg, R.** [US/US]; 1500 Oak Avenue, Los Al-  
tos, CA 94024 (US). **BECKER, Cyrus** [US/US]; 121 Lau-  
rel Avenue, Menlo Park, CA 94025 (US). **DRUZGALA,**  
**Pascal** [US/US]; 120 Hatona Drive, Santa Rosa, CA 95403  
(US).

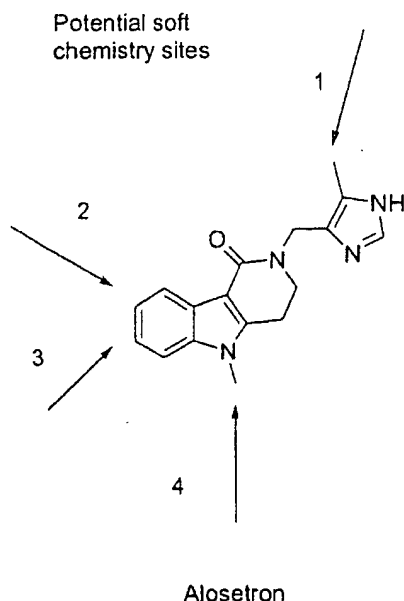
Published:

- with international search report
- before the expiration of the time limit for amending the  
claims and to be republished in the event of receipt of  
amendments

[Continued on next page]

(54) Title: 5-HT<sub>3</sub> RECEPTOR ANTAGONISTS AND METHODS OF USE

(57) Abstract: The subject invention provides useful and novel 5-HT<sub>3</sub>  
antagonists. The subject invention also provides methods for synthesiz-  
ing the compounds of invention. The invention also provides methods  
for the treatment of irritable bowel syndrome and other such conditions.



WO 03/061657 A1

AM2

WO 03/061657 A1

---



*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

DESCRIPTIONNOVEL 5-HT<sub>3</sub> RECEPTOR ANTAGONISTS AND METHODS OF USE

5

Cross-Reference to Related Application

This application claims the benefit of U.S. Provisional Application Serial No. 60/350,504, filed January 18, 2002.

10

Background of Invention

Irritable bowel syndrome (IBS) is one of the most common gastrointestinal disorder thought to result from dysregulation of intestinal motor, sensory and CNS function. In the United States, the estimated prevalence is 15% to 20%, and 75% of patients are women. Despite its prevalence, IBS is poorly understood. It is one of  
15 over 20 functional gastrointestinal (GI) disorders that are not explained by identifiable structural or biochemical abnormalities. IBS is characterized by persistent or recurrent symptoms of abdominal pain with diarrhea and/or constipation. IBS is believed to relate to abnormalities in motility and/or afferent sensitivity as mediated by the central nervous system. Patients with IBS have a diminished quality of life and  
20 use significant health care resources.

Treatment for patients diagnosed with IBS has included antidepressant drugs, tranquilizers and laxatives. Pharmacological intervention in diarrhea-predominant IBS focuses on the reduction of bowel motility, spasms and transit times. Peripherally acting opiod ligands such as the petidine congeners diphenoxylate and  
25 loperamide and the k-opiod agonist fedotozine slow gastrointestinal transit by their effects on the circular and longitudinal muscle. While these drugs show some effects on intestinal motility, their effects on IBS-related abdominal pain and intestinal relief is generally insufficient.

Alosetron, a selective 5-HT<sub>3</sub> receptor antagonist closely related to  
30 ondansetron in terms of chemistry and pharmacology, is the first compound of this type to be developed for irritable bowel syndrome. Alosetron and its uses are described in, for example, U.S. Patent No. 6,284,770, which is incorporated herein by reference. A number of different 5-HT<sub>3</sub> receptor antagonists have been disclosed, for

example those of group A: indisetron, Ro-93777, YM-114, granisetron, talipexole, azasetron, tropisetron, mirtazapine, ramosetron, ondansetron, lerisetron, alosetron, N-3389, zacopride, cilansetron, E-3620, lintopride, KAE-393, itasetron, mosapride and dolasetron.

5 In UK Patent No. 2209335 there is disclosed, inter alia, the compound 2,3,4,5-tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido [4,3-b]indol-1-one, now known as alosetron, and pharmaceutically acceptable salts, solvates and pharmaceutically acceptable equivalents thereof, in particular its hydrochloride salt.

5-HT<sub>3</sub> receptor antagonists are known to be useful in the treatment of a  
10 variety of conditions involving 5-HT<sub>3</sub> receptor-mediated mechanisms, including in particular emesis.

Ondansetron inhibits emesis by blocking 5-HT<sub>3</sub> receptors on vagal afferent nerve terminals in the gastrointestinal mucosa and on terminals on the same vagal nerves in the vomiting system located in the dorsal medulla of brain stem. Alosetron,  
15 in various animal models, can reduce the increase in intestinal fluid secretion and motility triggered by serotonin release. Alosetron increases sensory threshold to balloon distension of the rectum, either by a direct effect on afferent pain perception, or via an increase in rectal compliance. In addition, 5-HT<sub>3</sub> receptor antagonists have been shown to slow colonic transit in man (ondansetron and alosetron). Clinical data  
20 for up to 3 months of treatment indicate that alosetron was orally bioavailable and significantly superior to both placebo and the smooth muscle relaxant, mebeverine, in improving perception of visceral pain, spasms and diarrhea in female diarrhea-predominant IBS.

Alosetron received FDA approval for the treatment of IBS in women with  
25 diarrhea in early 2000. It is the first drug to have proven efficacy for IBS. Alosetron (Lotronex<sup>TM</sup>) was launched in the US, its first market and was also launched in Puerto Rico for the treatment of women with irritable bowel syndrome who have diarrhea as the predominant symptom. However, in November 2000, Glaxo Wellcome withdrew alosetron from the US market, prompted by reports of alosetron-associated ischaemic colitis (n = 49; characterized by abdominal cramping and pain)  
30 and severe constipation (n = 21). The FDA also received 3 reports of deaths which were associated with alosetron.

Alosetron has approximately 60% oral bioavailability and a half-life of 1.5 hours. Greater variability was seen in the pharmacokinetic profile in all parameters in females compared with males. Females also had 60% greater drug exposure than males, with mean peak plasma concentration 45-100% higher. This is attributed to lower clearance and volume of distribution in female population. Similar gender-specific differences have been reported for ondansetron. At least 12 metabolites were detected in urine, which were eliminated from plasma with half-lives of approximately 3 hours. 6-Hydroxy-alosetron, which is twice as potent as alosetron was not detected in plasma, however the limit of detection was 6-fold higher than the  $K_i$  for this metabolite.

The pattern of fecal and urinary elimination of alosetron and its metabolites is suggestive of enterohepatic recirculation of 6-OH-alosetron, resulting in "prolonged" low level exposure. In addition, 6-OH-alosetron glucuronide and a hydroxymethyl metabolite also have potent 5-HT<sub>3</sub> receptor binding affinity. The pharmacodynamic effects of these metabolites are unknown. Clearance was predominantly by metabolism and renal excretion. Mass balance studies with radiolabeled drug indicate that the concentration of circulating metabolite is at least 10 fold greater than that of alosetron, yet, two-thirds of the circulating radioactivity cannot be attributed to alosetron or its metabolites. This is due to slower elimination and smaller V<sub>d</sub> of the metabolites.

Over 1200 patients with IBS received alosetron for at least 12 weeks during the Phase II and III clinical trials. Constipation was the most commonly reported adverse event, occurring in 28% of those taking alosetron and in 3% of those on placebo. This side effect appears to be dose dependent and constipation occurred more frequently in female patients. This gender difference is perhaps related to the increased drug exposure level in the female patients.

Thus, it would be particularly desirable to find potent and selective 5-HT<sub>3</sub> antagonists having comparable pharmacodynamic effect to that of alosetron, with more predictable metabolism and an improved safety profile.

#### Brief Summary

The subject invention provides useful and novel 5-HT<sub>3</sub> antagonists and methods of use. The subject invention also provides methods for synthesizing the

compounds of the subject invention. In a specific embodiment, the subject invention also provides methods for the treatment of irritable bowel syndrome.

Advantageously, the subject invention provides compounds which are readily metabolized by the physiological metabolic drug detoxification systems. Specifically, in a preferred embodiment, the therapeutic compounds of the subject invention contain an ester group, which does not detract from the ability of these compounds to provide a therapeutic benefit, but which makes these compounds more susceptible to degradation by hydrolases, particularly serum and/or cytosolic esterases. The subject invention further provides methods of treatment comprising the administration of these compounds to individuals in need of 5-HT<sub>3</sub> antagonist treatment.

#### Brief Description of the Drawings

**Figure 1** shows the structures of three 5-HT<sub>3</sub> antagonists - alosetron, ondansetron, and granisetron.

**Figure 2** shows sites at which alosetron may be modified according to the subject invention to create analogs (soft chemistry sites) which have advantageous pharmacokinetic properties as described herein.

**Figure 3** shows specific analogs of the subject invention as well as the primary inactive metabolite after the active compound has been exposed to hydrolytic enzymes.

**Figure 4** shows specific analogs of the subject invention as well as the primary inactive metabolite after the active compound has been exposed to hydrolytic enzymes.

**Figure 5** shows specific analogs of the subject invention as well as the primary inactive metabolite after the active compound has been exposed to hydrolytic enzymes.

**Figure 6** shows an example of a synthetic scheme which can be used to synthesize certain specific analogs of the subject invention.

**Figure 7** shows an example of a synthetic scheme which can be used to synthesize certain specific analogs of the subject invention.

**Figure 8** shows an example of a synthetic scheme which can be used to synthesize certain specific analogs of the subject invention.

Detailed Disclosure

The subject invention provides novel 5-HT<sub>3</sub> receptor antagonists. In a preferred embodiment, the 5-HT<sub>3</sub> antagonists of the subject invention can be deactivated to a primary inactive metabolite by hydrolytic enzymes.

5        Compounds of the present invention can be advantageously used to treat individuals in need of treatment with a 5-HT<sub>3</sub> receptor antagonist. In a preferred embodiment, the compounds of the subject invention are used to treat patients suffering from gastrointestinal disorders as exemplified by irritable bowel syndrome. The compounds of the subject invention are particularly advantageous due to their  
10        predictable pharmacokinetics.

As used herein, the term "individual(s)" refers to a mammal to which is administered a compound or composition of the present invention. The mammal may be, for example a mouse, rat, pig, horse, rabbit, goat, pig, cow, cat, dog, or human. In a preferred embodiment, the individual is a human.

15        Granisetron and ondansetron are potent 5-HT<sub>3</sub> antagonists widely used for treating emesis induced by chemotherapy (Figure 1). While ondansetron was the first to demonstrate 5-HT<sub>3</sub> antagonism activity in the colon, thereby reducing the sensation of pain and transit of content through the colon, alosetron was the first compound of this type to be developed for irritable bowel syndrome.

20        In a specific embodiment, the present invention provides novel alosetron analogs that are preferentially metabolized by endogenous hydrolytic enzymes. The novel compounds are bioactive molecules having activity on the gastrointestinal tract and undergoing deactivation to primary inactive metabolites by hydrolytic enzymes.

Sites at which alosetron can be modified according to the subject invention are  
25        shown in Figure 2. Specific analogs of the subject invention, as well as the primary metabolites are shown in Figures 3-5.

Adverse drug-drug interactions (DDI), elevation of liver function test (LFT) values, and QT prolongation leading to torsades de pointes (TDP) are three major reasons why drug candidates fail to obtain FDA approval. All these causes are, to  
30        some extent, metabolism-based. A drug that has two metabolic pathways, one oxidative and one non-oxidative, built into its structure is highly desirable in the pharmaceutical industry. An alternate, non-oxidative metabolic pathway provides the treated subject with an alternative drug detoxification pathway (an escape route) when

one of the oxidative metabolic pathways becomes saturated or non-functional. While a dual metabolic pathway is necessary in order to provide an escape metabolic route, other features are needed to obtain drugs that are safe regarding DDI, TDP, and LFT elevations.

5        In addition to having two metabolic pathways, the drug should have a rapid metabolic clearance (short metabolic half-life) so that blood levels of unbound drug do not rise to dangerous levels in cases of DDI at the protein level. Also, if the metabolic half-life of the drug is too long, then the CYP450 system again becomes the main elimination pathway, thus defeating the original purpose of the design. In order  
10    to avoid high peak concentrations and rapidly declining blood levels when administered, such a drug should also be administered using a delivery system that produces constant and controllable blood levels over time.

The compounds of this invention have one or more of the following characteristics or properties:

- 15        1.        Compounds of the invention are metabolized both by CYP450 and by a non-oxidative metabolic enzyme or system of enzymes;
2.        Compounds of the invention have a short (up to four (4) hours) non-oxidative metabolic half-life;
3.        Oral bioavailability of the compounds is consistent with oral  
20    administration using standard pharmaceutical oral formulations; however, the compounds, and compositions thereof, can also be administered using any delivery system that produces constant and controllable blood levels over time;
4.        Compounds according to the invention contain a hydrolysable bond that can be cleaved non-oxidatively by hydrolytic enzymes;
- 25        5.        Compounds of the invention can be made using standard techniques of small-scale and large-scale chemical synthesis;
6.        The primary metabolites of compounds of this invention result from the non-oxidative metabolism of the compounds;
7.        The primary metabolites, regardless of the solubility properties of the  
30    parent drug, is, or are, soluble in water at physiological pH and have, as compared to the parent compound, a significantly reduced pharmacological activity;
8.        The primary metabolites, regardless of the electrophysiological properties of the parent drug, has, or have, negligible inhibitory activity at the  $IK_R$



(HERG) channel at normal therapeutic concentration of the parent drug in plasma (e.g., the concentration of the metabolite must be at least five times higher than the normal therapeutic concentration of the parent compound before activity at the  $IK_R$  channel is observed);

5           9.       Compounds of the invention, as well as the metabolites thereof, do not cause metabolic DDI when co-administered with other drugs;

          10.       Compounds of the invention, as well as metabolites thereof, do not elevate LFT values when administered alone.

          In some embodiments, the subject invention provides compounds that have  
10   any two of the above-identified characteristics or properties. Other embodiments provide for compounds having at least any three of the above-identified properties or characteristics. In another embodiment, the compounds, and compositions thereof, have any combination of at least four of the above-identified characteristics or properties. Another embodiment provides compounds having any combination of  
15   five to ten of the above-identified characteristics or properties. In a preferred embodiment, the compounds of the invention have all ten characteristics or properties.

          In various embodiments, the primary metabolites of the inventive compounds, regardless of the electrophysiological properties of the parent drug, has, or have, negligible inhibitory activity at the  $IK_R$  (HERG) channel at normal therapeutic  
20   concentrations of the drug in plasma. Preferably, the concentration of the metabolite must be at least five times higher than the normal therapeutic concentration of the parent compound before activity at the  $IK_R$  channel is observed. Preferably, the concentration of the metabolite must be at least ten times higher than the normal therapeutic concentration of the parent compound before activity at the  $IK_R$  channel is  
25   observed.

          Compounds according to the invention are, primarily, metabolized by endogenous hydrolytic enzymes via hydrolysable bonds engineered into their structures. The primary metabolites resulting from this metabolic pathway are water soluble and do not have, or show a reduced incidence of, DDI when administered with  
30   other medications (drugs). Non-limiting examples of hydrolysable bonds that can be incorporated into compounds according to the invention include amide, ester, carbonate, phosphate, sulfate, urea, urethane, glycoside, and other bonds that can be cleaved by hydrolases.

Additional modifications of the compounds disclosed herein can readily be made by those skilled in the art. Thus, analogs and salts of the exemplified compounds are within the scope of the subject invention. With a knowledge of the compounds of the subject invention skilled chemists can use known procedures to synthesize these compounds from available substrates. The accompanying figures show certain specific compounds including those substituted with lower (C<sub>1-4</sub>) alkyl. The person skilled in the art having the benefit of the instant disclosure would appreciate that other substituents could be made in order to arrive at other compounds having the advantageous biological activity (5-HT<sub>3</sub> receptor antagonist) and pharmacokinetic properties.

As used in this application, the term "analogs" refers to compounds which are substantially the same as another compound but which may have been modified by, for example, adding additional side groups. The term "analogs" as used in this application also may refer to compounds which are substantially the same as another compound but which have atomic or molecular substitutions at certain locations in the compound.

Analog of the exemplified compounds can be readily prepared using commonly known, standard reactions. These standard reactions include, but are not limited to, hydrogenation, methylation, acetylation, and acidification reactions. For example, new salts within the scope of the invention can be made by adding mineral acids, *e.g.*, HCl H<sub>2</sub>SO<sub>4</sub>, *etc.*, or strong organic acids, *e.g.*, formic, oxalic, *etc.*, in appropriate amounts to form the acid addition salt of the parent compound or its derivative. Also, synthesis type reactions may be used pursuant to known procedures to add or modify various groups in the exemplified compounds to produce other compounds within the scope of the invention.

The subject invention further pertains to enantiomerically isolated compounds, and compositions comprising the compounds, for 5-HT<sub>3</sub> antagonism. The isolated enantiomeric forms of the compounds of the invention are substantially free from one another (*i.e.*, in enantiomeric excess). In other words, the "R" forms of the compounds are substantially free from the "S" forms of the compounds and are, thus, in enantiomeric excess of the "S" forms. Conversely, "S" forms of the compounds are substantially free of "R" forms of the compounds and are, thus, in enantiomeric excess of the "R" forms. In one embodiment of the invention, the isolated

enantiomeric compounds are at least about in 80% enantiomeric excess. In a preferred embodiment, the compounds are in at least about 90% enantiomeric excess. In a more preferred embodiment, the compounds are in at least about 95% enantiomeric excess. In an even more preferred embodiment, the compounds are in at least about 97.5% enantiomeric excess. In a most preferred embodiment, the compounds are in at least 99% enantiomeric excess.

A further aspect of the subject invention pertains to the breakdown products which are produced when the therapeutic compounds of the subject invention are acted upon by hydrolytic enzymes, such as esterases. The presence of these breakdown products in urine or serum can be used to monitor the rate of clearance of the therapeutic compound from a patient.

The compounds of this invention have therapeutic properties similar to those of the unmodified parent compounds. Accordingly, dosage rates and routes of administration of the disclosed compounds are similar to those already used in the art and known to the skilled artisan (see, for example, *Physicians' Desk Reference*, 54<sup>th</sup> Ed., Medical Economics Company, Montvale, NJ, 2000).

The compounds of the subject invention can be formulated according to known methods for preparing pharmaceutically useful composition. Formulations are described in detail in a number of sources, which are well known and readily available to those skilled in the art. For example, *Remington's Pharmaceutical Science* by E.W. Martin describes formulation, which can be used in connection with the subject invention. In general, the compositions of the subject invention are formulated such that an effective amount of the bioactive compound(s) composition.

In accordance with the subject invention, pharmaceutical compositions are provided which comprise, as an active ingredient, an effective amount of one or more of the compounds and one or more non-toxic, pharmaceutically acceptable carriers or diluents. Examples of such carriers for use in the invention include ethanol, dimethyl sulfoxide, glycerol, silica, alumina, starch, and equivalent carriers and diluents. Further, acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories and dispersible granules. A solid carrier can be one or more substances, which may act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents or encapsulating materials.

The disclosed pharmaceutical compositions may be subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, such as packeted tablets, capsules, and powders in paper or plastic containers or in vials or ampoules. Also, the unit dosage can be a liquid based preparation or formulated to be incorporated into solid food products, chewing gum, or lozenges.

The subject invention further provides methods of synthesizing the unique and advantageous therapeutic compounds of the subject invention. Particularly, methods of producing less toxic therapeutic agents comprising introducing ester groups into therapeutic agents are taught. The ester linkage may be introduced into the compound at a site which is convenient in the manufacturing process for the compounds of the invention. Various exemplary synthetic routes for the preparation of the compounds of the subject invention are described in Figures 6-8. Additionally, the sensitivity of the ester linkage may be manipulated by the addition of side groups which hinder or promote the hydrolytic activity of the hydrolases or esterases responsible for cleaving the drug at the ester locus. Methods of adding such side groups, as well as the side groups themselves, are well known to the skilled artisan and can be readily carried out utilizing the guidance provided herein.

All patents, patent applications, provisional applications, and publications referred to or cited herein are incorporated by reference in their entirety, including all figures and tables, to the extent they are not inconsistent with the explicit teachings of this specification.

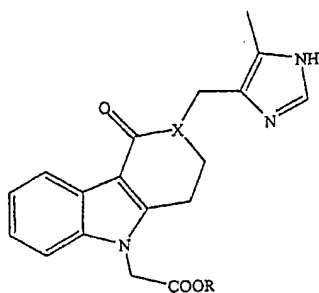
It should be understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application.

Claims

We claim:

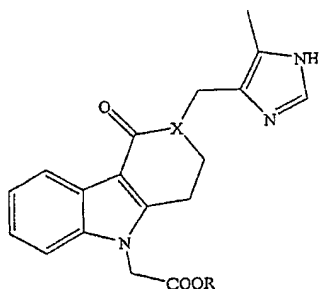
1. A 5-HT<sub>3</sub> receptor antagonist having at least one characteristic chosen from the group consisting of:
  - a. the compound is metabolized both by CYP450 and by a non-oxidative metabolic enzyme or system of enzymes;
  - b. the compound has a short (up to four (4) hours) non-oxidative metabolic half-life;
  - c. the compound contains a hydrolysable bond that can be cleaved non-oxidatively by hydrolytic enzymes;
  - d. the primary metabolites of the compound result from the non-oxidative metabolism of the compound;
  - e. the primary metabolites are soluble in water at physiological pH;
  - f. the primary metabolites have negligible inhibitory activity at the I<sub>K<sub>R</sub></sub> (HERG) channel at normal therapeutic concentration of the parent drug in plasma;
  - g. the compound, as well as the metabolites thereof, does not cause metabolic DDI when co-administered with other drugs; and
  - h. the compound, as well as metabolites thereof, does not elevate LFT values when administered alone.

2. The compound, according to claim 1, wherein said compound has the following structure, or is an analog or a salt of a compound having the following structure:



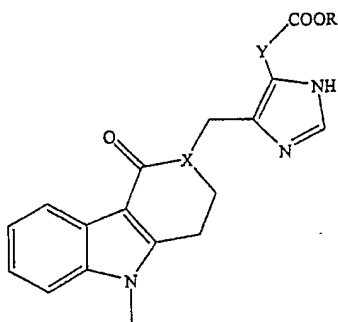
$\text{X} = \text{N}$ , or  $\text{CH}$   
 $\text{R}$  = lower alkyl optionally substituted  
with  $\text{OH}$  or  $\text{NH}_2$ .

3. The compound, according to claim 2, having the following formula:



$\text{X} = \text{N}$ , or  $\text{CH}$   
 $\text{R}$  = lower alkyl optionally substituted  
with  $\text{OH}$  or  $\text{NH}_2$ .

4. The compound, according to claim 1, wherein said compound has the following structure, or is an analog or a salt of a compound having the following structure::

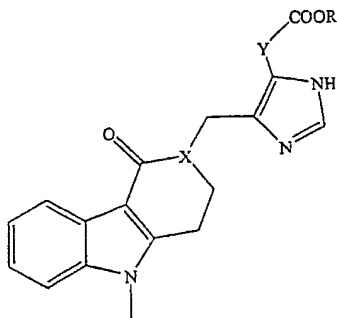


X = CH, or N

Y = (CH<sub>2</sub>)<sub>n</sub>

R = lower alkyl optionally substituted with  
OH or NH<sub>2</sub>.

5. The compound, according to claim 4, having the following structure:

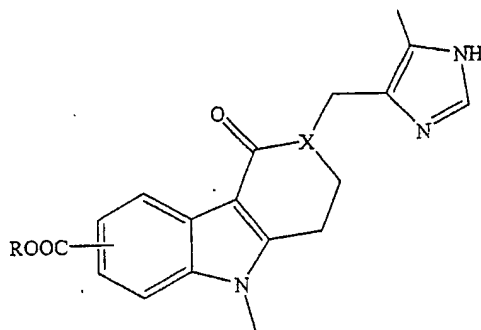


X = CH, or N

Y = (CH<sub>2</sub>)<sub>n</sub>

R = lower alkyl optionally substituted with  
OH or NH<sub>2</sub>.

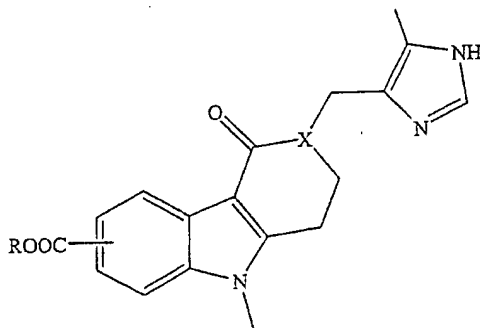
6. The compound, according to claim 1, wherein said compound has the following structure, or is an analog or a salt of a compound having the following structure:



X = CH, or N

R = lower alkyl optionally substituted  
with OH or NH<sub>2</sub>.

7. The compound, according to claim 6, having the following structure:



X = CH, or N

R = lower alkyl optionally substituted  
with OH or NH<sub>2</sub>.

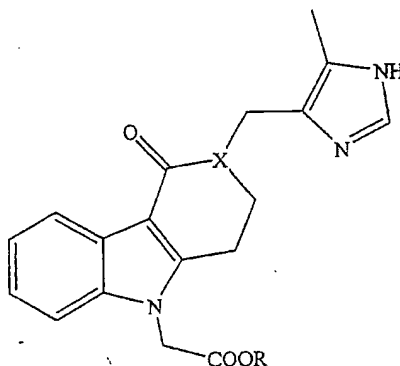
8. A pharmaceutical composition comprising a 5-HT<sub>3</sub> receptor antagonist having at least one characteristic chosen from the group consisting of:

- the compound is metabolized both by CYP450 and by a non-oxidative metabolic enzyme or system of enzymes;
- the compound has a short (up to four (4) hours) non-oxidative metabolic half-life;



- c. the compound contains a hydrolysable bond that can be cleaved non-oxidatively by hydrolytic enzymes;
  - d. the primary metabolites of the compound result from the non-oxidative metabolism of the compound;
  - e. the primary metabolites are soluble in water at physiological pH;
  - f. the primary metabolites have negligible inhibitory activity at the  $IK_R$  (HERG) channel at normal therapeutic concentration of the parent drug in plasma;
  - g. the compound, as well as the metabolites thereof, does not cause metabolic DDI when co-administered with other drugs; and
  - h. the compound, as well as metabolites thereof, does not elevate LFT values when administered alone;
- wherein said composition further comprises a pharmaceutical carrier.

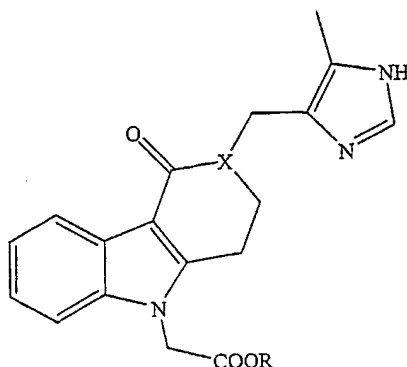
9. The pharmaceutical composition, according to claim 8, comprising a compound, or an analog or salt thereof, wherein said compound has the following structure:



$X = N$ , or  $CH$

$R$  = lower alkyl optionally substituted with  $OH$  or  $NH_2$ .

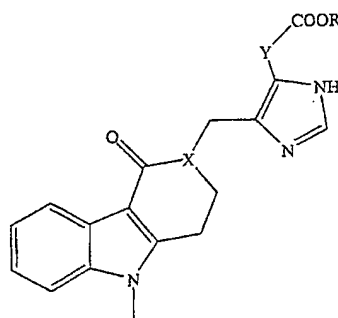
10. The composition, according to claim 10, comprising a compound having the following structure:



X = N, or CH

R = lower alkyl optionally substituted with OH or NH<sub>2</sub>.

11. The composition, according to claim 8, comprising a compound or an analog or salt thereof, wherein said compound has the following structure:

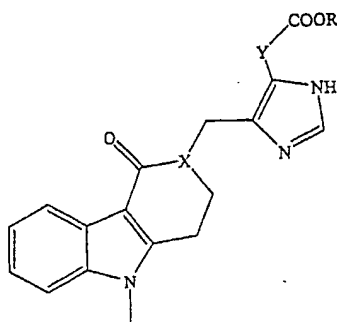


X = CH, or N

Y = (CH<sub>2</sub>)<sub>n</sub>

R = lower alkyl optionally substituted with OH or NH<sub>2</sub>.

12. The composition, according to claim 11, comprising a compound having the following structure:

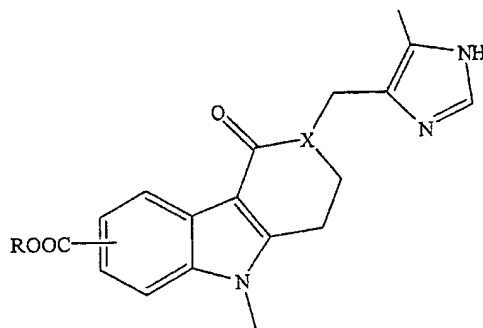


X = CH, or N

Y = (CH<sub>2</sub>)<sub>n</sub>

R = lower alkyl optionally substituted with OH or NH<sub>2</sub>.

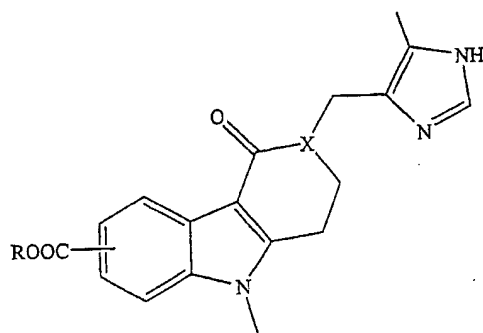
13. The composition, according to claim 1, comprising a compound, or an analog or salt thereof, wherein said compound has having the following structure:



X = CH, or N

R = lower alkyl optionally substituted with OH or NH<sub>2</sub>.

14. The composition, according to claim 13, comprising a compound having the following structure:

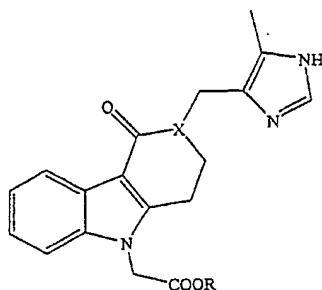


$\text{X} = \text{CH}$ , or  $\text{N}$

$\text{R}$  = lower alkyl optionally substituted with  $\text{OH}$  or  $\text{NH}_2$ .

15. A method for blocking 5-HT<sub>3</sub> activity in a patient in need of such treatment wherein said method comprises administering to said patient a 5-HT<sub>3</sub> blocking compound having at least one of the following characteristics:
- the compound is metabolized both by CYP450 and by a non-oxidative metabolic enzyme or system of enzymes;
  - the compound has a short (up to four (4) hours) non-oxidative metabolic half-life;
  - the compound contains a hydrolysable bond that can be cleaved non-oxidatively by hydrolytic enzymes;
  - the primary metabolites of the compound result from the non-oxidative metabolism of the compound;
  - the primary metabolites are soluble in water at physiological pH;
  - the primary metabolites have negligible inhibitory activity at the  $\text{IK}_R$  (HERG) channel at normal therapeutic concentration of the parent drug in plasma;
  - the compound, as well as the metabolites thereof, does not cause metabolic DDI when co-administered with other drugs; and
  - the compound, as well as metabolites thereof, does not elevate LFT values when administered alone.

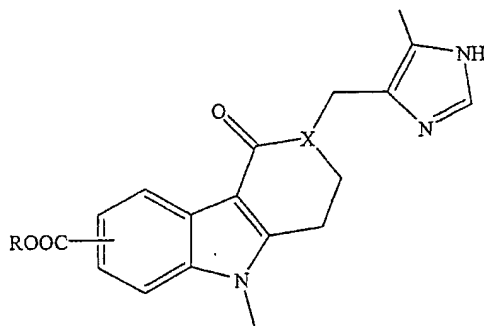
16. The method, according to claim 15, comprising administering a compound, or an analog or salt thereof, wherein said compound has the following structure:



X = N, or CH

R = lower alkyl optionally substituted  
with OH or NH<sub>2</sub>.

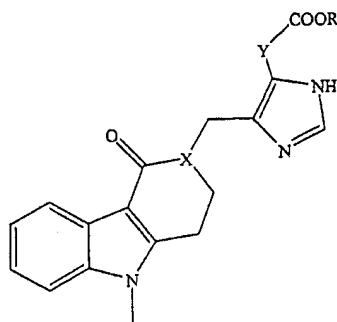
17. The method, according to claim 16, wherein said compound has the following formula:



X = CH, or N

R = lower alkyl optionally substituted  
with OH or NH<sub>2</sub>.

18. The method, according to claim 15, comprising administering a compound, or an analog or salt thereof, wherein said compound has the following structure:

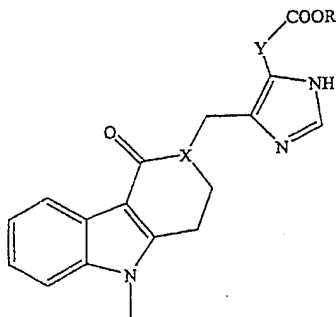


X = CH<sub>2</sub>, or N

Y = (CH<sub>2</sub>)<sub>n</sub>

R = lower alkyl optionally substituted with  
OH or NH<sub>2</sub>.

19. The method, according to claim 18, wherein said compound has the following structure:

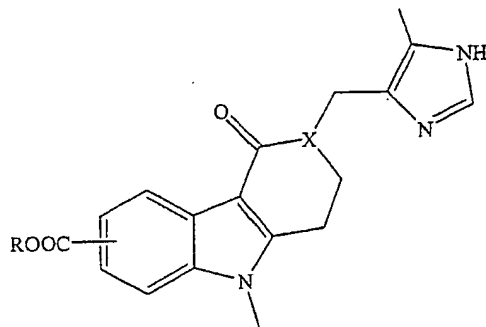


X = CH<sub>2</sub>, or N

Y = (CH<sub>2</sub>)<sub>n</sub>

R = lower alkyl optionally substituted with  
OH or NH<sub>2</sub>.

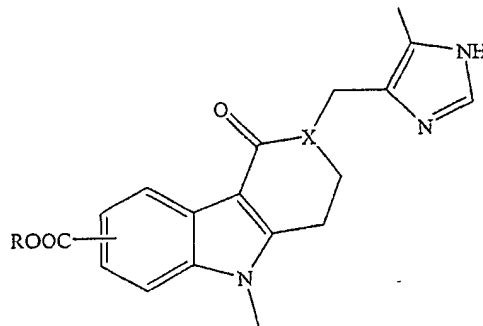
20. The method, according to claim 15, comprising administering a compound, or an analog or salt thereof, wherein said compound has the following structure:



X = CH, or N

R = lower alkyl optionally substituted with OH or NH<sub>2</sub>.

21. The method, according to claim 20, wherein said compound has the following structure:



X = CH, or N

R = lower alkyl optionally substituted with OH or NH<sub>2</sub>.

22. The method, according to claim 15, wherein the patient is human.

23. The method, according to claim 15, wherein said method is used to treat irritable bowel syndrome.

1/6

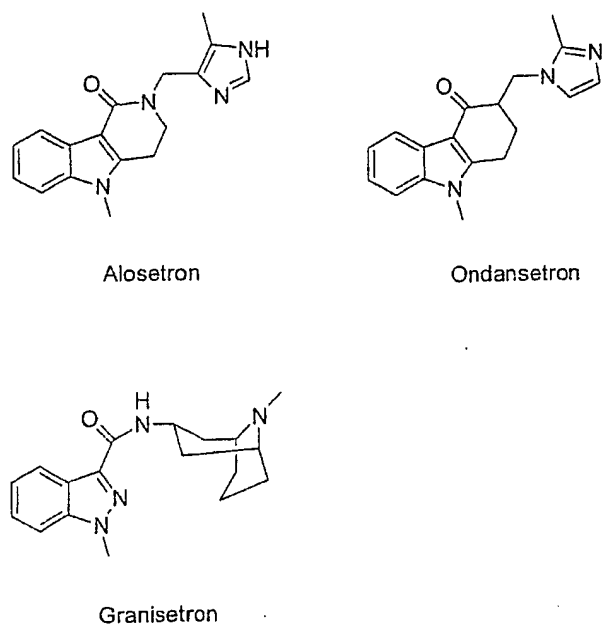


FIG. 1

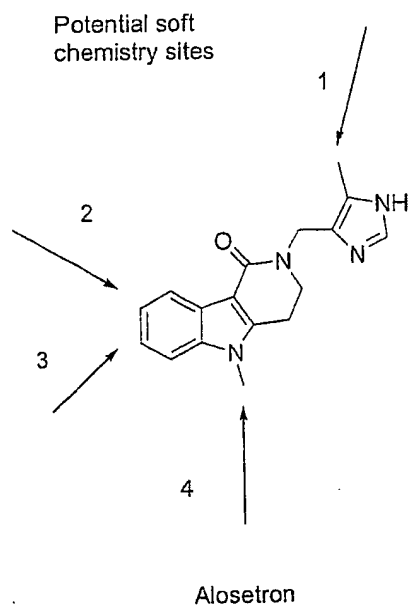
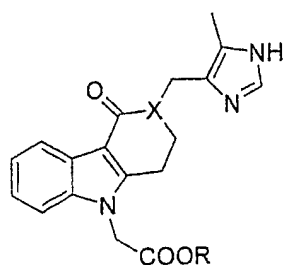


FIG. 2



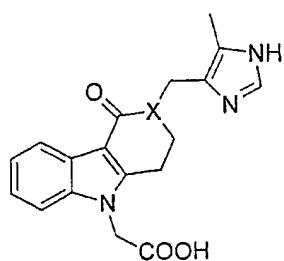
2/6



X=N, or CH  
R= lower alkyl optionally substituted  
with OH or NH<sub>2</sub>.

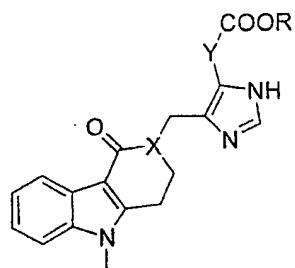


Hydrolytic enzymes



Primary inactive metabolite

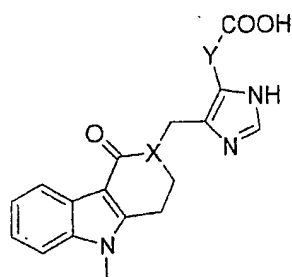
FIG. 3



X=CH, or N  
Y=(CH<sub>2</sub>)<sub>n</sub>  
R=lower alkyl optionally  
substituted with OH or NH<sub>2</sub>



Hydrolytic enzymes

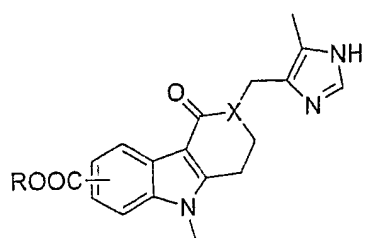


X=CH, or N  
Y=(CH<sub>2</sub>)<sub>n</sub>

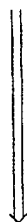
Primary inactive metabolite

FIG. 4

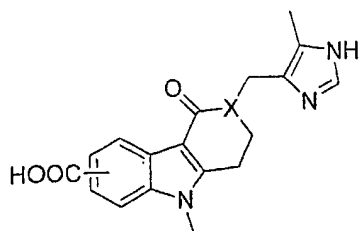
3/6



X=CH, or N  
R=lower alkyl optionally  
substituted with OH or NH<sub>2</sub>



Hyrolytic enzymes



X=CH, or N  
Primary inactive metabolite

FIG. 5

4/6

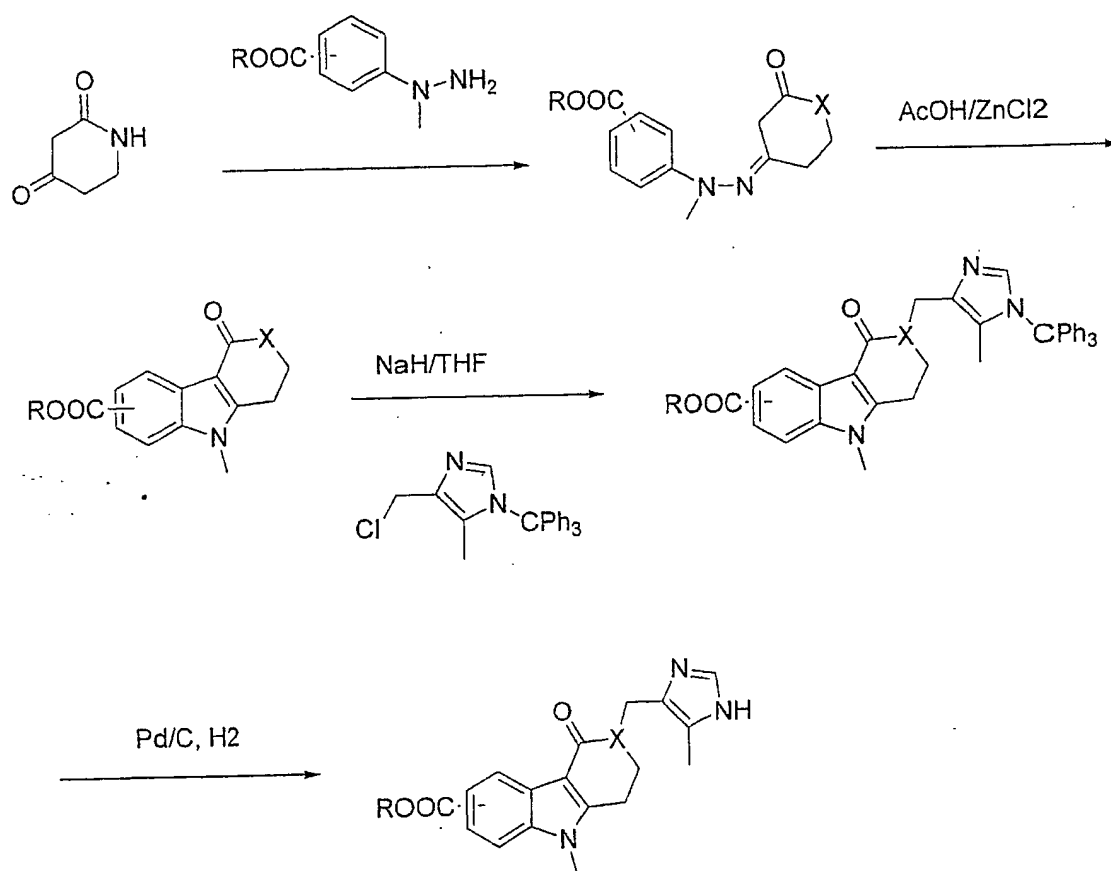


FIG. 6

5/6

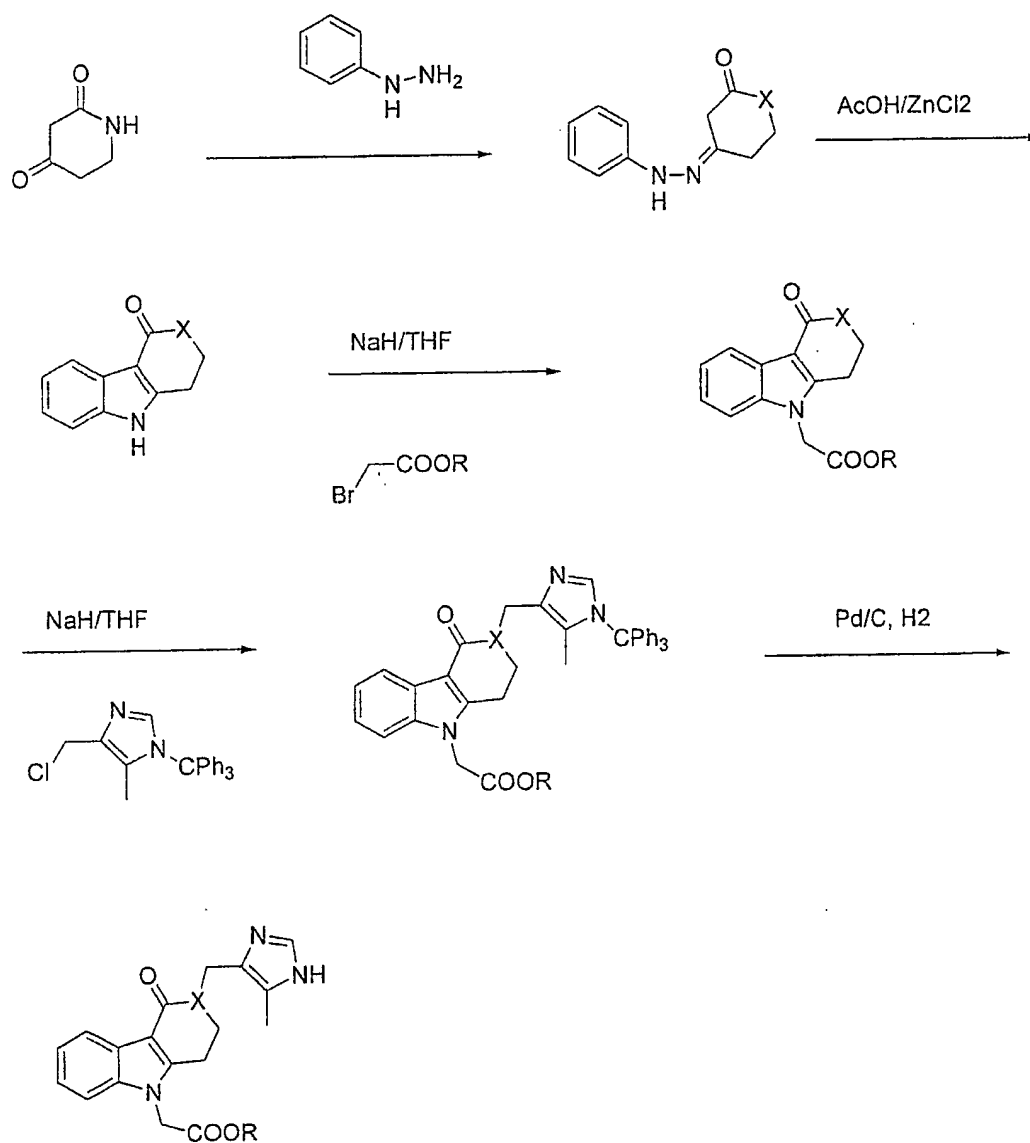


FIG. 7

6/6

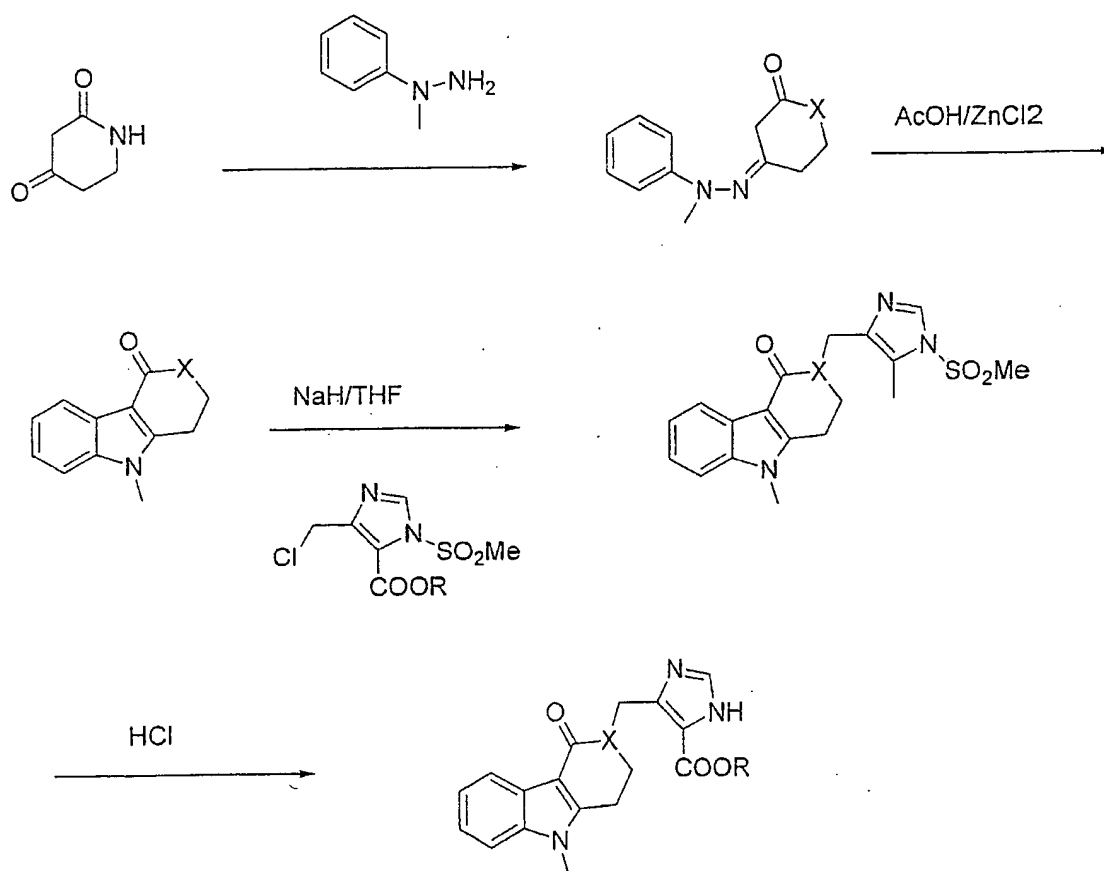


FIG. 8

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 03/01876

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 7 A61K31/444 A61P1/04 C07D471/04 //(C07D471/04,221:00,  
209:00)

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 7 A61K A61P C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE, CHEM ABS Data, BEILSTEIN Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 202 343 A (PRICE BARRY J ET AL) 13 April 1993 (1993-04-13) column 1, line 54 -column 2, line 40; example 16 column 35, line 37 -column 38, line 40 column 5, line 12 ---	1-23
X	EP 0 353 983 A (GLAXO GROUP LTD) 7 February 1990 (1990-02-07) page 5, line 11; claims 1,4; examples 19,20 -----	1-23

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*Z\* document member of the same patent family

Date of the actual completion of the international search

4 June 2003

Date of mailing of the international search report

16/06/2003

Name and mailing address of the ISA  
European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Härtinger, S

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US 03/01876

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
Although claims 15-23 are directed to a method of treatment of the human body, the search has been carried out and based on the alleged effects of the compound, however, which the restriction indicated for claims 1 and 8.
2. ☒ Claims Nos.: 1(part), 8(part)  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 03/01876

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 5202343	A	13-04-1993	AT 396933 B	27-12-1993
			AT 312487 A	15-05-1993
			AU 605805 B2	24-01-1991
			AU 8184587 A	02-06-1988
			BE 1001004 A4	06-06-1989
			CA 1326032 A1	11-01-1994
			CH 676120 A5	14-12-1990
			CN 87107308 A , B	08-06-1988
			CZ 9104045 A3	11-08-1993
			DE 3740352 A1	09-06-1988
			DK 624887 A	29-05-1988
			EG 18509 A	28-02-1994
			ES 2008360 A6	16-07-1989
			FI 875235 A , B ,	29-05-1988
			FR 2611366 A1	02-09-1988
			GB 2202530 A , B	28-09-1988
			GR 871809 A1	07-03-1988
			HK 51591 A	12-07-1991
			HU 45993 A2	28-09-1988
			IE 61510 B1	16-11-1994
			IL 84635 A	31-01-1993
			IT 1211936 B	08-11-1989
			JP 63211279 A	02-09-1988
			KR 9609433 B1	19-07-1996
			MX 9517 A	01-11-1993
			NL 8702851 A	16-06-1988
			NO 874959 A , B ,	30-05-1988
			NZ 222725 A	28-08-1990
			PH 30436 A	09-05-1997
			PL 269095 A1	01-09-1988
			PT 86230 A , B	01-12-1987
			SE 467255 B	22-06-1992
			SE 8704746 A	29-05-1988
			SG 46591 G	26-07-1991
			SU 1731047 A3	30-04-1992
			US 4822881 A	18-04-1989
			US 4859662 A	22-08-1989
			YU 217487 A1	31-08-1989
			ZA 8708923 A	26-10-1988
			ZW 22587 A1	19-10-1988
			AT 102940 T	15-04-1994
			AU 633254 B2	28-01-1993
			AU 3499189 A	23-11-1989
			DE 68913816 D1	21-04-1994
			DE 68913816 T2	30-06-1994
			DK 245789 A	21-11-1989
			EP 0345956 A1	13-12-1989
			FI 892415 A	21-11-1989
EP 0353983	A	07-02-1990	HU 56567 A2	30-09-1991
			AT 138659 T	15-06-1996
			AU 631131 B2	19-11-1992
			AU 3918689 A	08-02-1990
			CA 1336906 A1	05-09-1995
			DE 68926553 D1	04-07-1996
			DE 68926553 T2	17-10-1996
			DK 377889 A	03-02-1990
			EP 0353983 A2	07-02-1990



# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 03/01876

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0353983 A		ES 2088389 T3	16-08-1996
		FI 893634 A ,B,	03-02-1990
		GR 3020349 T3	30-09-1996
		IL 91167 A	10-06-1993
		JP 2160786 A	20-06-1990
		NO 893101 A ,B,	05-02-1990
		NZ 230154 A	25-10-1991
		PT 91336 A ,B	08-03-1990
		US 5183820 A	02-02-1993
		ZA 8905859 A	29-08-1990

Continuation of Box I.2

Claims Nos.: 1(part),8(part)

Present claims 1 and 8 relate to a product or composition defined merely by reference to a series of desirable characteristics or properties, namely features which are related to certain biological metabolic pathways. The claims cover all products and compositions having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of alosetron or ondansetron analogous. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the product or composition by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the products having the general formulae depicted in the figures 3 to 8.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.